I. Response to Restriction Requirement under 35 U.S.C. 121

The pending claims have been subjected to a Restriction Requirement as follows:

Group I, claims 1-10, drawn to a pharmaceutical composition, classified in 424, subclass 735;

Group II, claims 11-16, drawn to a method for administering the pharmaceutical composition of claim 1, classified in class 424, subclass 780.

The Examiner suggests that Groups I and II as set forth above are distinct, each from the other, because each invention is directed to divergent subject matter with different features. Further, the Examiner suggests that due to the separate status given to the Groups, the search for prior art would not be co-extensive between the groups.

Applicants respectfully traverse this restriction requirement.

MPEP §803 is quite clear; for a proper restriction requirement, it must be shown (1) that the inventions are independent or distinct AND (2) that there would be a serious burden on the Examiner if the restriction is not required. MPEP 802.01 defines "distinct" to mean that the "two or more subjects as disclosed are related, for example, as combination and part (subcombination) thereof, process and apparatus for its practice,

process and product made there, etc., but are capable of separate manufacture, use, or sale, as claimed, AND ARE PATENTABLE (novel and unobvious) OVER EACH OTHER."

All of claims of the instant application relate to the concept of a pharmaceutical composition comprising a prebiotic, a probiotic and a urea degrading microorganism. Accordingly, each of the claims contain the same components, and each of the claims are useful for the same endpoint, i.e. a composition useful for renal, hepatic and gastrointestinal diseases. Further, claims 11-16 are dependent upon claim 1. Thus, Applicants respectfully disagree that the Groups set forth by the Examiner are distinct as being novel and unobvious over each other, as required by MPEP § 802.01.

Further, a search of literature relating to a pharmaceutical composition comprising a prebiotic, a probiotic and a urea degrading microorganism would clearly reveal art relating to both of these Groups. Thus, the inclusion of both Groups in this application would not be overly burdensome to the Examiner. Accordingly, the instant Restriction Requirement meets neither of the criteria as set forth by MPEP §803 to be proper.

Reconsideration and withdrawal of this Restriction Requirement is therefore respectfully requested.

However, in an earnest effort to be completely responsive, Applicants hereby affirm election of Group I, claims 1-10 with traverse.

II. Rejection of Claims 3, 5, 7 and 8 Under 35 U.S.C. §112, second paragraph

The Examiner has rejected claims 3, 5, 7 and 8 under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner suggests that claims 3, 5, 7 and 8 are vague and indefinite because it is unclear if Applicants intend to use a Markush group. In an earnest effort to advance prosecution, Applicants have amended claims 3, 5, 7 and 8 in accordance with the language suggested by the Examiner.

The Examiner has also rejected the phrase "the inorganic phosphate adsorbent" in claim 5, line 2 as lacking antecedent basis. Applicants have amended claim 5, line 2 to clarify the invention as supported throughout the specification and especially at page 16. Reconsideration and withdrawal of these rejections is hereby requested.

III. Rejection of Claims 1-3 and 6-9 Under 35 U.S.C. §102

The Examiner has rejected claim 1-3 and 6-9 under 35 U.S.C. §102 as being anticipated by Cavadini et al. (US 5,968,569). The Examiner suggests that the Applicants claim a pharmaceutical composition comprising a probiotic, prebiotic and an ammonia-philic urea degrading microorganism with high alkaline stability and urease activity, that is microencapsulated or enteric coated. The composition further comprises a water adsorbent selected from locust bean gum, psyllium fiber, guar gum and zeolite.

The Examiner suggests that Cavadini et al. teach compositions comprising encapsulated probiotic microorganisms selected from *Bifidobacterium, Bacillus* and *Lactobacillus* and fiber selected from inulin, fructooligosaccharides, guar gum, and carob bean gum. Applicants respectfully traverse this rejection.

A general level of operability is required in a reference to establish a *prima facie* case of obviousness or anticipation. See MPEP § 2121. In accordance with MPEP § 2121.01, the test in determining that quantum of prior art disclosure which is necessary to declare an applicant's invention "not novel" or "anticipated" within section 102, is whether a reference contains an "enabling disclosure". *In re Hoeksema*, 399 F.2d 269(CCPA 1968). A reference

contains an "enabling disclosure" if the public was in possession of the claimed invention before the date of invention.

The instant invention is a microencapsulated or enteric coated pharmaceutical composition comprising a probiotic, a prebiotic and an ammoniaphilic urea degrading microorganism, wherein the entire composition is microencapsulated or enteric-coated. Claim 1 has been amended to clarify that the microencapsulated or enteric coating material is designed to deliver the probiotic, a prebiotic, and ammoniaphilic urea degrading microorganism to their site of action in relatively native form without binding of various digestive materials to the sorbents prior to reaching the target region, and prevent infection of a patient from the ammoniaphilic urea degrading microorganism.

Cavadini et al. teach pet food products, more specifically, ready-to-eat cereals which contain probiotic microorganisms. The probiotic microorganism is carried in the coating on the cereal. See column 2, lines 20-25. There is no teaching of a composition of a probiotic, a prebiotic and an ammoniaphilic urea degrading microorganism, wherein the entire composition is microencapsulated or enteric-coated. Further, there is no teaching that any coating material prevents infection of a patient from the ammoniaphilic

urea degrading microorganism. Accordingly, Cavadini et al. cannot anticipate the instant invention.

Applicants respectfully request reconsideration and withdrawal of this rejection.

IV. Rejection of Claims Under 35 U.S.C. §103

The Examiner has rejected claim 1-3 and 6-9 under 35 U.S.C. §103(a) as unpatentable over Paul (US 6,180, 099) in view of Ford (US 5,733,568).

The Examiner suggests that Paul teaches a composition comprising inulin, guar gum, fructo-oligosaccharides and a bacteria selected from *Lactobacillus* and *Bifidobacteria* for gastrointestinal health. However, as acknowledged by the Examiner, Paul does not teach the microorganisms are ammoniaphilic and urea-degrading with high alkaline stability and urease activity. The Examiner also acknowledges that Paul does not teach encapsulated or enteric coatings.

The Examiner suggests that Ford teaches that micro-encapsulating *Lactobacilli* to protect them from gastric juices. The Examiner suggests that it would have been obvious to encapsulate the composition of Paul, as it was common to do so, as demonstrated by Ford. Applicants respectfully disagree.

At the onset it is respectfully pointed out that claim 1 has been amended to clarify that the composition comprises a probiotic, a prebiotic, and an ammoniaphilic urea degrading microorganism with high alkaline pH stability and high urease activity. The composition is microencapsulated or enteric coated with a material designed to deliver a probiotic, a prebiotic, and ammoniaphilic urea degrading microorganism to their site of action in relatively native form without binding of various digestive materials to the sorbents prior to reaching the target region, and prevent infection of a patient from the ammoniaphilic urea degrading microorganism, as supported throughout the specification and especially at pages 15-16.

To establish a *prima facie* case of obviousness under 35 U.S.C. 103(a) three basic criteria must be met. MPEP § 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all of the claim limitations.

Paul teaches a composition for promoting gastrointestinal health which may include *Lactobacillus* and *Bifidobacterium*,

comprising 40-60% by weight of an immunoglobulin composition and 40-60% by weight of soluble dietary fiber. Paul teaches that the microorganisms are *intended* to bind to and inactivate foreign antigens,pathogenic bacteria, viruses, fungi, and protozoa in the gastrointestinal tract. See column 1, lines 19-35. As admitted by the Examiner, Paul does not teach any microencapsulated or enteric coating at all.

Ford teaches a composition particularly useful for treating vaginal infections which comprises microencapsulated *Lactobacilli*. The microencapsulated coating of the *Lactobacilli* is taught to increase their shelf life and further to release the bacteria into the intestine as the microencapsulation material is taught to lose its structural integrity. Ford does not teach composition comprising a probiotic, a prebiotic, and an ammoniaphilic urea degrading microorganism with high alkaline pH stability and high urease activity.

The recited art fails to teach all of the limitations of claim 1. Neither Paul nor Ford teach composition comprising a composition being microencapsulated or enteric coated with a material designed to deliver the probiotic, a prebiotic, and ammoniaphilic urea degrading microorganism to their site of action in relatively native form without binding of various digestive

materials to the sorbents prior to reaching the target region, and prevent infection of a patient from the ammoniaphilic urea degrading microorganism. Accordingly, the references fail to establish a *prima facie* case of obviousness against the pending claims 1-10.

Further, the compositions of both Paul and Ford teach away from the present invention. Paul teaches a composition intended to bind to other molecules upon ingestion, which is inapposite to the present invention which is specifically coated to deliver the probiotic, a prebiotic, and ammoniaphilic urea degrading microorganism to their site of action in relatively native form without binding of various digestive materials to the sorbents prior to reaching the target region. Ford teaches a composition comprising a bacteria with a microencapsulated coating, in which the coating is *intended* to release the bacteria into the intestine of a patient as microencapsulation material loses its structural integrity. Ford's teaching is also inapposite to the present invention which teaches a coating designed to prevent the microorganism from entering or infecting a patient. Thus, even if these teachings were combined the result would not successfully produce the present invention.

Further, one skilled in the art would not be motivated to combines these references, as one reference is a food stuff and the other is a vaginal preparation. There would be no motivation to combine the two to produce a composition such as the present invention, and even if they were combined they would not result in the claimed invention. Withdrawal of this rejection is respectfully requested.

The Examiner has further rejected claims 1-10 under 35 U.S.C. §103(a) as unpatentable over Paul (US 5,531,988) in view of Ash et al.(US 4,581,141), Hider et al (US 5, 698, 190) Yatzidis (1979) and Niisato(JP 59,110,621).

The Examiner suggests that the cited art discloses a pharmaceutical composition comprising a probiotic, prebiotic and an ammonia-philic urea-degrading microorganism with high alkaline stability and urease activity that is microencapsulated or enteric coated. Applicants respectfully disagree.

The Examiner suggests that Paul teaches a composition for promoting gastrointestinal health comprising an effective amount of *Lactobacillus* and *Bifidobacterium*. The Examiner further suggests that Paul teaches *Lactobacillus* and *Bifidobacteria* inhibit toxic activities of bacteria in patients with chronic kidney failure,

inhibit overgrowth of gastrointestinal pathogens and reduce pathogenic microorganism titers in the gastro-intestinal tract.

The Examiner also suggests that Ash et al. teach compositions containing charcoal and zeolite for removing uremic substances. Specifically, Ash et al. are suggested to teach that charcoal is an adsorbent for uremic substances to include guanidines, creatine, uric acid, drugs, phenols, organic acids, and middle molecules. Ash et al. are additionally suggested to teach that charcoal is inefficient in removing water and phosphate and suggests that a complete sorbent dialyzer must include other sorbents for such substances such as zeolite.

Hider is suggested to teach that patients with kidney disorders who suffer from elevated phosphate levels are tested with magnesium hydroxide, aluminum hydroxide, calcium hydroxide or mixtures thereof.

Yatzidis is suggested to teach locust bean gum is an efficient sorbent upon uremic substances to include urea, chloride, uric acid, creatine, ammonia, phosphorous and sodium.

Niisato et al. are suggested to teach a composition containing fructooligosaccharides for preventing uremia and renal insufficiency.

Ford (US 5,733,568) is suggested to teach that microencapsulating *Lactobacilli* protect the bacteria from gastric juices and allows then to reach lower intestines where they are therapeutically beneficial.

The Examiner suggests that it would have been obvious to one of ordinary skill in the art to have combined the ingredients for their known benefit. And further, that it would have been obvious to one of skill in the art to microencapsulate the ingredients as taught by Ford, as it was routine at the time of the invention. Applicants respectfully traverse this rejection.

It is respectfully pointed out that claims 1 and 10 have been amended to clarify that the composition comprises a probiotic, a prebiotic, and an ammoniaphilic urea degrading microorganism with high alkaline pH stability and high urease activity. Further, the composition is microencapsulated or enteric coated with a material designed to deliver the probiotic, a prebiotic, and ammoniaphilic urea degrading microorganism to their site of action in relatively native form without binding of various digestive materials to the sorbents prior to reaching the target region, and prevent infection of a patient from the ammoniaphilic urea degrading microorganism, as supported throughout the specification and in particular at pages 15-16.

None of the recited prior art provides any reasonable expectation of success of making a composition being microencapsulated or enteric coated. More particularly, none of the references teach any enteric or microencapsulated coating material designed to deliver the probiotic, a prebiotic, and ammoniaphilic urea degrading microorganism to their site of action in relatively native form without binding of various digestive materials to the sorbents prior to reaching the target region, and which prevents infection of a patient from the ammoniaphilic urea degrading microorganism.

Paul teaches an oral composition for promoting gastrointestinal health which include a bacteria and an immunoglobulin-containing composition. *Lactobacillus* and *Bifidobacterium* may be included in the composition. Paul teaches that the microorganisms are effective when administered orally. Paul teaches that a composition containing a mixture of the immunoglobulin composition and beneficial bacteria has a synergistic effect in causing death of the pathogenic microorganisms and in restoring gastrointestinal health. Regular consumption of the bacteria and immunoglobulin-containing composition are taught to have the effect of maintaining good

gastrointestinal health. Paul does not teach any enteric or microencapsulated coating in the composition.

Ash et al. teach compositions for use in dialysis machines. The composition can containing charcoal and zeolite for removing uremic substances. Ash does not teach the ingestion of any composition by a patient. Ash does not teach any microencapsulated coating on the composition.

Hider et al. teach a polymer containing guanidino groups which are capable of specifically binding to phosphate and reducing the uptake of phosphate from the diet of kidney patients. The polymer is taught to be incorporated into food stuff. Hider et al. do not teach any pharmaceutical composition comprising a probiotic, a prebiotic, and an ammoniaphilic urea degrading microorganism with high alkaline pH stability and high urease activity. Hider et al. do not teach any microencapsulated coating or enteric coating.

Yatzidis et al. teach that locust bean gum is a sorbent upon uremic substances including urea. Yatzidis et al. further teach that ingestion of locust bean gum is impracticable because it swells in the mouth and the esophagus. See page 105. Yatzidis et al. teach a mixture of cottonseed oil and locust bean gum mixed with cottonseed oil to allow ingestion. Yatzidis et al. do not teach any pharmaceutical composition comprising a probiotic, a

prebiotic, and an ammoniaphilic urea degrading microorganism with high alkaline pH stability and high urease activity. Yatzidis et al. do not teach any microencapsulated or enteric coating.

Niisato et al. teach a strong diuretic composition containing fructooligosaccharides for preventing uremia and renal insufficiency. Niisato et al. do not teach a composition of a probiotic, a prebiotic, and an ammoniaphilic urea degrading microorganism with high alkaline pH stability and high urease activity. Niisato et al. do not teach any composition being microencapsulated or enteric coated.

As discussed above, Ford teaches a composition particularly useful for treating vaginal infections which comprises microencapsulated *Lactobacilli*. The microencapsulated coating of the *Lactobacilli* is taught to increase their shelf life and further to release the bacteria into the intestine as the microencapsulation material loses its structural integrity. Ford does not teach composition comprising a probiotic, a prebiotic, and an ammoniaphilic urea degrading microorganism with high alkaline pH stability and high urease activity. Ford does not teach any enteric coating. Ford does not teach any microencapsulated coating which prevents the microorganisms from infecting the patient.

None of the recited art, with the exception of Ford, teach compositions having any enteric or microencapsulated coating. Ford teaches a microencapsulated coating which releases a microorganism into the patient. Accordingly, none of the references teach any coating material designed to deliver the probiotic, a prebiotic, and ammoniaphilic urea degrading microorganism to their site of action in relatively native form without binding of various digestive materials to the sorbents prior to reaching the target region, and prevent infection of a patient from the ammoniaphilic urea degrading microorganism, as recited in independent claims 1 and 10, the references fail to establish a *prima facie* case of obviousness against the pending claims 1-10.

Further, one of skill in the art would not be motivated to combine these recited references together.

Paul teaches an oral composition useful for causing the death of pathogenic microorganisms. Hider et al teach a polymer which may be incorporated into food stuff. Yatzidis et al. teach a sorbent which is generally impracticable for oral ingestion, and therefor only capable of administration in limited quantities. Niisato et al. teach a diuretic composition.

By contrast, Ash et al. teach compositions useful in dialysis machines. Ash et al. do not teach any oral compositions.

Ford, teaches a composition for treatment of vaginal infections comprising a coating designed to release bacteria into the intestine of the patient.

A skilled artisan would not be motivated to combine references teaching oral compositions with references teaching compositions for dialysis machines. Further, even if all of the recited references were combined, they would not teach or suggest all of the limitations of the claimed invention. Namely, only one reference, Ford, teaches any type of microencapsulated coating. However, The coating taught by Ford is inapposite to the coating of the present invention in that Ford intends for the coating to allow microorganisms into the intestines of the patient, whereas the present invention is intended to prevent the microorganisms from entering or infecting the patient. Further, a skilled artisan would refrain from incorporating an enteric or microencapsulated coating into the composition taught by Paul because the un-coated composition taught by Paul comprises an immunoglobulin composition and beneficial bacteria in specified ratios which provides a synergistic effect in causing death of the pathogenic microorganisms. There is no motivation to add a coating to this composition as the synergistic effect may be altered.

MPEP § 2143 and the Courts are quite clear; both the teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The cited combination of prior art fails to provide this reasonable expectation of success. It is only with the instant specification in hand, which demonstrates the efficacy of Applicants' invention that one of skill has a reasonable expectation of success.

Withdrawal of this rejection is respectfully requested.

CONCLUSION

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**."

Respectfully submitted,

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Date: **September 3, 2002**

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MARKED UP VERSION TO SHOW CHANGES MADE

In the claims:

Claims have been amended as follows:

1. (amended) A pharmaceutical composition comprising a composition of a probiotic, a prebiotic, and an ammoniaphilic urea degrading microorganism with high alkaline pH stability and high urease activity, said composition being microencapsulated or enteric coated with a material designed to deliver the probiotic, a prebiotic, and ammoniaphilic urea degrading microorganism to their site of action in relatively native form without binding of various digestive materials to the sorbents prior to reaching the target region, and prevent infection of a patient from the ammoniaphilic urea degrading microorganism.

3. (amended) The pharmaceutical composition of claim 2 where the water absorbent is selected from the group consisting of locust bean gum, psyllium fiber, guar gum and zeolite.

5. (amended) The pharmaceutical composition of claim 4 wherein the sorbent for inorganic phosphate ~~adsorbent~~ is selected from the group consisting of aluminum hydroxide gel, calcium hydroxide gel and magnesium hydroxide gel and the specific uremic solute adsorbent is activated charcoal.

7. (amended) The pharmaceutical composition of claim 1 wherein the prebiotic is selected from the group consisting of fructan oligosaccharide and araban oligosaccharide.

8. (amended) The pharmaceutical composition of claim 1 wherein the ammoniaphilic bacteria is selected from the group consisting of *Bacillus pasteurii*, *Sporosarcina ureae*, *Bacillus* species and *Lactobacillus* species KB-I.

10. (amended) A pharmaceutical composition comprising a probiotic, a prebiotic, an ammoniaphilic urea degrading microorganism with high alkaline pH stability and high urease activity, a water absorbent, a sorbent for inorganic phosphate and an adsorbent for specific uremic solutes other than urea, said composition being microencapsulated or enteric coated with a material designed to deliver the probiotic, a prebiotic, and ammoniaphilic urea degrading microorganism to their site of action in relatively native form without binding of various digestive materials to the sorbents prior to reaching the target region, and prevent infection of a patient from the ammoniaphilic urea degrading microorganism.